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A Placental Cause of Intra-uterine Fetal Death Depends on the Perinatal Mortality Classification System Used

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Abstract

Different classification systems for the cause of intra-uterine fetal death (IUFD) are used internationally. About two thirds of these deaths are reported as unexplained and placental causes are often not addressed. Differences between systems could have consequences for the validity of vital statistics, for targeting preventive strategies and for counselling parents on recurrence risks. Our objective was to compare use of the Tulip classification with other currently used classification systems for causes of IUFD. We selected the extended Wigglesworth classification, modified Aberdeen and the classifications by Hey, Hovatta, de Galan-Roosen and Morrison. We also selected the ReCoDe system for relevant conditions, comparable to contributing factors in the Tulip classification. Panel classification for 485 IUFD cases in the different systems was performed by assessors after individual investigation of structured patient information. Distribution of cases into cause of death groups for the different systems varied, most of all for the placental and unknown groups. Systems with a high percentage of cases with an unknown cause of death and death groups consisting of clinical manifestations only are not discriminatory. Our largest cause of death group was placental pathology and classification systems without placental cause of death groups or minimal subdivision of this group are not useful in modern perinatal audit as loss of information occurs. The most frequent contributing factor was growth restriction. This illustrates the vital role of the placenta in determination of optimal fetal development. In the Tulip classification, mother, fetus and placenta are addressed together. The system has a clear defined subclassification of the placenta group, a low percentage of unknown causes and is easily applied by a multidisciplinary team. A useful classification aids future research into placental causes of IUFD.

Keywords: Placental cause of death; Classification system; Intra-uterine fetal death; Antepartum stillbirth

1. Introduction

There are intensified demands on medical, political and epidemiological grounds for proper determination and classification of cause of perinatal death [1–5]. The largest subgroup of perinatal mortality worldwide is the stillbirth group consisting of intra-uterine fetal deaths (IUFD) and intrapartum deaths. Current use of classification systems for analyses of this subgroup consistently report of about two thirds of these deaths as being unexplained [6]. Classification of cause of death is needed for the individual patient in the process of mourning, for the purpose of counselling and prevention and for the comparison of health care nationally and internationally. Classification of IUFD is complex due to the complicated pathophysiological processes encountered in the mother, fetus and placenta, and as a result of their interaction [7]. The multiplicity of contributing factors and the different background of the clinicians involved, adds to the complexity.

Different classification systems have been designed for different reasons with different approaches, definitions, levels of complexity and availability of guidelines. No single system is universally accepted and each has strengths and weaknesses

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[8,9]. Problems occur during use and comparison of different systems. Our research group developed a new classification system for perinatal mortality: the Tulip classification, in anticipation of current needs [8]. This system was designed by a multidisciplinary panel. Placental causes of death formed our largest cause of death group. This is in accordance with others who also found placental causes of death in up to 60% of perinatal mortality cases [2,10–13]. However, availability of a placental death group varies in internationally used classification systems.

Our goal for this study was to investigate underlying cause of death for an IUFD group after evaluation of clinical and diagnostic information. Special interest was in placental causes. Our objective was to compare use of the Tulip classification with other currently used classification systems for IUFD. Question was whether information is gained or lost by classification in the different systems. This could have consequences for counselling parents on recurrence risks, for targeting placental research and preventive strategies, and for the validity of vital statistics.

2. Materials and methods

In 2002 we initiated a national study on IUFD at the University Medical Centre in Groningen (UMCG) with 50 participating hospitals throughout the Netherlands. Inclusion criteria for the study were singleton IUFD's diagnosed antepartum after 20 weeks of gestation. For each included IUFD a case record form was filled in and a standard diagnostic work-up protocol was performed.

Patient information sets included baseline characteristics such as date of delivery, gestational age, medical and obstetric history; maternal characteristics; fetal characteristics including fetal and placental weights at birth; pregnancy details and obstetric discharge letters. Apart from these characteristics, diagnostic test results were available including: pathological findings concerning autopsy and placental investigation; maternal blood tests; maternal viral serology; fetal blood tests; fetal viral serology; cultures from mother, fetus and placenta; and chromosomal investigation. Autopsy and placental examination were performed by local pathologists in participating hospitals after parental consent was obtained. No national pathological guidelines regarding autopsy and placental examination after IUFD exist, therefore we urged participating pathologists to follow our study guidelines for autopsy and placental examination based on the guidelines published by the Royal College of Obstetricians and Gynaecologists [14] and the Royal College of Pathologists and the College of American Pathologists [15,16].

After patient sets were made as complete as possible panel classification sessions were initiated. Procedures were agreed upon in advance. For fetal and placental weights at birth gestational age at determination of IUFD was used. Small for gestational age (SGA) was defined as birth weight $<$10th percentile [17]. Placenta hypoplasia was defined as an absolute too low placenta weight $<$10th percentile and/or a too low placenta/birth weight ratio [18]. We defined placental bed pathology for preterm cases as any infarctions found at placental histology and for term cases as extensive infarction that affected $>$10% of the placental area [19]. Cause of death "placental bed pathology" was allocated if in our opinion the percentage of infarcted parenchyma in relation to the weight of the placenta was severe enough to cause death. The classification panel consisted of two obstetricians, an obstetric resident, and a paediatric pathologist. All panel members prepared each case individually using the patient information sets where after panel discussions were held and a panel consensus on cause of death was agreed upon. No other information sources were consulted. Only one underlying cause of death could be allocated. For each classification system we added "problematic classification" as cause of death group. This cause was classified if allocation of cause of death caused confusion for a system and/or two causes of death groups could be allocated at the same time.

3. Used classification systems for cause of death

After panel discussion on the basis of use of existing classifications and current obstetric, pathologic and genetic literature on causes of IUFD we selected six classification systems besides the Tulip classification. These systems represent different approaches of classification with different definitions. The selected systems were as follows: the extended Wigglesworth [20], the modified Aberdeen [21], classification by Hey et al. [22], by Hovatta et al. [23], by de Galan-Roosen et al. [24] and by Morrison and Olsen [25]. The reason for choice of the system as well as the system itself will be discussed in the following paragraphs.

The *Tulip* classification is a single cause classification system aiming to identify the initial demonstrable pathophysiological entity initiating the chain of events that has irreversibly led to death. Cause of death is based on the combination of clinical findings and diagnostic test results, including pathological findings for the purpose of counselling and prevention [8]. As our goal was to particularly focus on placental causes of death we discuss this part of the guideline.

3.1. Placental cause of death

Cause of death is explained by a placental pathological abnormality supported by the clinical findings.

1. *Placental bed pathology*. Inadequate spiral artery remodelling and/or spiral artery pathology is leading to uteroplacental vascular insufficiency such as placental infarction and abruption.
2. *Placental pathology*. Placental pathology originated during development of the placenta itself, abnormalities in the parenchyma or localisation of the placenta.
    a. *Development*. Morphologic abnormalities arise because of abnormal developmental processes. Examples: placenta circumvallata, vasa praevia, villus immaturity, and placenta hypoplasia.
    b. *Parenchyma*. Acquired placenta parenchyma disorders of the villi or intervillous space. Examples: fetal thrombotic vasculopathy, maternal floor infarct, villitis of unknown origin, massive perivillous fibrin deposition and fetomaternal haemorrhage without obvious cause.
    c. *Abnormal localisation*. Examples: placenta praevia.
3. *Umbilical cord complication*. Example: true knot with occlusion of the umbilical vessels.
4. *Not otherwise specified*. The cause of death can be allocated to the group placenta but, because of the combination of different placenta subclassifications, a choice cannot be made as to what was first in the chain of events leading to death.

The *extended Wigglesworth* classification, the *modified Aberdeen* and the classification by *Hey et al.* [20–22] are based on the earliest developed classification systems. These systems have different approaches and are the most commonly

used systems for British statistics [3]. In addition, both the extended Wigglesworth and the modified Aberdeen [20,21] are most widely used throughout the world [26–31]. Wigglesworth's advocated a pathophysiological approach and the goal of the classification is to subdivide cases into groups with clear implications for priorities for prevention and alterations in clinical management. The modified Aberdeen is a clinicopathological classification, the first version was proposed by Baird et al. [21] and aim is to classify each death in accordance with the factor which probably initiated "the train of events ending in death". It is almost entirely based on clinical information as in the experience of the designers of the system post-mortem examinations fail to explain cause of death in many cases. The classification by Hey et al. [22] is based on the bound classification [32,33]. This classification has a pathologic approach based on fetal and neonatal entities and aim is to define the clinicopathological process within the baby and the way they contribute to, and help to explain the baby's death. *Hovatta et al*. [23] designed a system especially for the group of stillbirths. Aim is to classify underlying cause of death considering both clinical and autopsy findings. The classification groups are based on maternal, fetal, placental or a combination of these entities. Definitions for the placental causes, however, do not exist.

The classification by *de Galan-Roosen et al*. is one of the few systems based on maternal, fetal and placental entities [24]. Aim is to serve prevention and classify underlying cause of death with a clinicopathological approach based on the entities that initiated the chain of events leading to death. The group placenta pathology is defined as follows in the guideline.

1. *Acute/subacute placental pathology*: total or partial abruption of the placenta, placental haematomata with intervillous thrombosis, marginal haemorrhage, subchorial haematoma, placental infarction >10%, velamentous insertion with vasolaceration or compression of the cord, and cord prolapse/compromise. Sometimes no placenta pathology can be found. Clinical manifestations in the fetus are signs of asphyxia with (in the subacute phase) time to aspirate meconium-stained amniotic fluid.
2. *Chronic/progressive placental pathology*: placental maldevelopment like in placenta praevia, uterine malformation or septum. Maternal circulation disorders and terminal villus deficiency like in pregnancy-induced hypertension (PIH), pre-eclampsia, and thrombophilia. Also when coagulation disorders are found in blood samples of the mother like in systemic lupus erythematosus (SLE). Examples: massive perivillous fibrin depositions, villitis of unknown origin, and diabetic changes in the placenta: pale, large and immature villi with oedema. Clinical manifestations of chronic placenta pathology in the fetus can be signs of small for gestational age.

The classification by *Morrison and Olsen* [25] is especially designed for stillbirths based on the clinicopathological classification of the British perinatal mortality survey [34,35]. The major contributing cause of death selected is based on maternal entities with an obstetric clinical approach and divided into specific weight categories. Aim is to serve prevention and study or define implications for that geographical area or clinic studied. Their group *hypoxia*; *placental insufficiency* is defined as: "autopsy evidence of hypoxia with appropriate weight for gestation, with meconium or meconium-stained membranes in vertex presentation; or birth weight/placental weight ratio >7:1 or placental infarcts >25%". The group *hypoxia*; *cord accidents/compression* is defined as: "nuchal cord ≥2, or true knot, or prolapse, or perforation at amniocentesis".

4. Relevant conditions

The latest published classification is the system by Gardosi et al. in 2005 [3]. Their ReCoDe classification seeks to establish relevant conditions at death taking into account mother, fetus and placenta. This system is not designed for allocation of cause of death. From the start of our panel sessions we classified contributing factors for the Tulip classification besides cause of death. Our contributing factors are defined as other known factors on the causal pathway to death, e.g. risk factors. These contributing factors are very similar to ReCoDe's relevant conditions. Combining information from our Tulip causes of death and contributing factors it was therefore possible to classify relevant conditions according to the ReCoDe classification.

5. Results

During the 4-year period of 2002–2006 we included 485 IUFD's. Median gestational age was 31 weeks and 4 days (range 20–42 weeks, 1 day). Median age of the mother was 30 years (range 18–46 years). Of the 485 IUFD's 263 were boys, 221 girls and for one case sex at birth could not be determined and no information on chromosomal or pathological examination was available. Autopsy was performed in 348 (71.7%) cases and external macroscopic fetal examination by a pathologist without autopsy in 18 cases (3.7%). Placental examination was performed in 481 cases (99.1%). The extent to which the placental examination guidelines were followed differed between cases.

During the panel sessions all IUFD's were classified according to the eight selected classification systems. For the *Tulip* classification distribution of causes of death is shown in Table 1. Largest cause of death group for 312 cases was placenta (64.3%). Largest placenta subgroups were placental bed pathology in 166 cases (34.2%) and placental pathology/development in 76 cases (15.7%). No cases were allocated to the group prematurity as we studied on IUFD cohort. Eight cases were allocated to the infection group. In 113 cases (23.3%) cause of death remained unknown, and in 30 cases important information was missing.

Distribution of causes of death for the *extended Wigglesworth* the *modified Aberdeen*, the classification by *Hey et al*., by *Hovatta et al*., by *de Galan-Roosen et al*. and by *Morrison et al*. are shown in Tables 2–7, respectively. Relevant

Table 1
Tulip classification: causes

Cause of death	*n* (% of total)	Subclassification		*n*
1. Congenital anomaly	28 (5.8)	1. Chromosomal defect	1. Numerical	12
			2. Structural	2
			3. Microdeletion/uniparental disomy	–
		2. Syndrome	1. Monogenic	–
			2. Other	2
		3. Central nervous system		–
		4. Heart and circulatory system		3
		5. Respiratory system		–
		6. Digestive system		1
		7. Urogenital system		–
		8. Musculoskeletal system		–
		9. Endocrine/metabolic system		–
		10. Neoplasm		3
		11. Other	1. Single organ	–
			2. Multiple organ	5
2. Placenta	312 (64.3)	1. Placental bed pathology		166
		2. Placental pathology	1. Development	76
			2. Parenchyma	16
			3. Localisation	–
		3. Umbilical cord complication		25
		4. Not otherwise specified		29
3. Prematurity/immaturity	–	1. PPROM		–
		2. Preterm labour		–
		3. Cervical incompetence		–
		4. Iatrogenous		–
		5. Not otherwise specified		–
4. Infection	8 (1.7)	1. Transplacental		5
		2. Ascending		3
		3. Neonatal		–
		4. Not otherwise specified		–
5. Other	24 (4.9)	1. Fetal hydrops of unknown origin		16
		2. Maternal disease		8
		3. Trauma	1. Maternal	–
			2. Fetal	–
		4. Out of the ordinary		–
6. Unknown	113 (23.3)	1. Despite thorough investigation		83
		2. Important information missing		30
Total	100			485

Table 2
Extended Wigglesworth: causes

Code	Classification	%	Subclassification	*n*
1.0	Congenital defect/ malformation	6.0		29
2.0	Unexplained antepartum fetal death	88.5		429
3.0	Death from intrapartum asphyxia, anoxia or trauma	–		–
4.0	Immaturity	–		–
5.0	Infection	1.6		8
6.1	Due to other specific causes	3.7	Fetal conditions	18
6.2			Neonatal conditions	–
6.3			Paediatric conditions	–
7.0	Due to accident or non-intrapartum trauma	–		–
8.0	Sudden infant deaths, cause unknown	–		–
9.0	Unclassifiable	0.2		1
10.0	Problematic classification	–		–
Total		100		485

conditions for our 485 cases according to the *ReCoDe* classification by Gardosi et al. are shown in Table 8.

The extended Wigglesworth and the modified Aberdeen, which are amongst the internationally most used classification systems have an excessive number of unexplained cases and do not include placental causes of death in their system (Table 9). The Tulip system illustrates that a large group of these unexplained deaths have a placental cause of death. For the modified Aberdeen 293 cases were ''unexplained'' and four cases were ''problematic''. Contrary, eight ''unknown'' cases in the Tulip classification were allocated a known cause in the modified Aberdeen: congenital anomaly ($n = 1$); pre-eclampsia ($n = 1$); antepartum haemorrhage ($n = 2$) and maternal disorder ($n = 4$). For the extended Wigglesworth classification 429 cases were ''unexplained'' and one case was ''problematic'', and one case classified as ''unknown'' in the Tulip classification was classified as congenital defect/malformation in the Wigglesworth.

Table 3
Modified Aberdeen: causes

Code	Classification	%	Subclassification	n
01	Congenital anomaly	6.6	Neural tube defects	2
02			Other anomalies	30
03	Isoimmunisation	–	Due to rhesus (D) antigen	–
04			Due to other antigens	–
05	Pre-eclampsia	6.4	Pre-eclampsia without APH	28
06			Pre-eclampsia complicated by APH	3
07	Antepartum haemorrhage (APH)	9.3	With placenta praevia	1
08			With placental abruption	38
09			Of uncertain origin	6
10	Mechanical	4.1	Cord prolapse or compression with vertex or face presentation	18
11			Other vertex or face presentation	–
12			Breech presentation	–
13			Oblique or compound presentation, uterine rupture etc.	2
14	Maternal disorder	8.7	Maternal hypertensive disease	10
15			Other maternal disease	24
16			Maternal infection	8
17	Miscellaneous	3.7	Neonatal infection	–
18			Other neonatal disease	–
19			Specific fetal conditions	18
20	Unexplained	60.4	Equal or greater than 2.5 kg	90
21			Less than 2.5 kg	203
22	Unclassified	–	Unclassifiable	–
23	Problematic classification	0.8		4
Total		100		485

Table 4
Classification by Hey et al.: causes

Code	Classification	%	Subclassification	n
01	Congenital anomaly	6.0	Chromosomal defect	13
02			Inborn error of metabolism	–
03			Neural tube defect	1
04			Congenital heart defect	3
05			Renal abnormality	–
06			Other malformation	12
07	Isoimmunisation			–
08	Asphyxia	88.4	Antepartum	429
09			Intrapartum	–
10	Birth trauma			–
11	Pulmonary immaturity			–
12	Hyaline membrane disease (HMD)			–
13			With IVH	–
14			With infection	–
15	Intracranial haemorrhage		Intraventricular haemorrhage	–
16			Other intracranial bleeding	–
17	Infection	1.9	Necrotising enterocolitis	–
18			Antepartum	9
19			Intrapartum	–
20			Postpartum	–
21	Miscellaneous	3.7	Miscellaneous	18
22	Unclassifiable or unknown		Cot death	–
23			Unattended delivery	–
24			Other undocumented death	–
25	Problematic classification			–
Total		100		485

The largest group in the Tulip classification consisted of placental causes: 312 cases (64.3%). We plotted the Tulip placental causes against the causes of death in classification systems with at least one placental cause of death category [23–25]. The classifications by Hovatta et al., de Galan-Roosen et al. and Morrison et al. have fewer unexplained cases than the other used systems. These systems contain placental causes of death but as illustrated in Table 10 there is minimal subclassification of these categories. Besides, some causes of death groups represent clinical conditions which raise confusion.

6. Discussion

In anticipation of audit purposes and further international comparison of causes we investigated different classification systems for cause of IUFD. Our focus was on placental causes of death as these are becoming more and more recognized. We describe comparison of eight classification systems. The Tulip classification has an extensive subdivision of the placental group, a high percentage of cases with a ''known'' cause of death and cause of death groups do not consist of clinical manifestations of pathophysiological entities. In the other described systems, we encountered problems concerning at least one of these items resulting in loss of specific information.

The pathophysiology of IUFD is complex and involves maternal, fetal as well as placental entities. In order to assign a cause of death these entities should be addressed together. The main focus of this study was on placental causes of death. Four of the seven classification systems we used have a placental cause of death group [8,23–25]. In these systems except

Table 5
Classification by Hovatta et al.: causes

Code	Classification	%	Subclassification	n
1.0	Abruption of the placenta	7.8		38
2.0	Large placental infarction	21.9		106
3.0	Cord complication	5.2		25
4.1	Other placental feature	27.2	Severe pre-eclampsia	5
4.2			Cholestasis of pregnancy	1
4.3			Twin pregnancy	–
4.4			Immature birth	–
4.5			Severe maternal trauma	–
4.6			Uterine anomaly	–
4.7			Other causes	126
5.0	Asphyxia for unexplained reasons	8.2		40
6.0	Maternal isoimmunisation	–		–
7.1	Fetal bleeding	1.2	Fetofetal transfusion	–
7.2			Fetomaternal transfusion	5
7.3			Other bleeding	1
8.0	Severe chorioamnionitis	1.0		5
9.0	Major malformations	5.8		28
10.0	Unexplained	19.4		94
11.0	Problematic classification	2.3		11
Total		100		485

Table 6
Classification by de Galan-Roosen et al.: causes

Code	Classification	%	Subclassification	Specification	*n*
1.1.0	Trauma	–	Antenatal		–
1.2.0			At birth		–
1.3.0			Postnatal		–
2.1.1	Infection	1.7	Antenatal	Haematogenous	5
2.1.2				Transamniotic	3
2.2.0			Postnatal		–
3.1.0	Placenta/cord pathology	44.5	Acute/subacute		98
3.2.0			Chronic/progressive		118
4.1.0	Maternal immune system pathology	–	Blood type incompatibility		–
4.2.0			Blood platelet antibody		–
5.1.0	Congenital malformations incompatible with life	4.9	Hereditary		–
5.2.0			Non-hereditary		24
6.1.0	Prematurity/immaturity complications	–	Cervix incompetence		–
6.2.0			Preterm labour iatrogenous		–
6.3.0			Preterm labour ECI		–
7.1.0	Unclassifiable	26.6	Despite thorough examination		99
7.2.0			Important information missing		30
8.0.0	Problematic classification	22.3			108
Total		100			485

for the classification by Morrison et al. a placental cause of death was the largest death group varying from 44.5% for de Galan-Roosen et al. to 64.3% in the Tulip classification. This is in accordance with our previous study [8] and earlier published data [2,10–13]. A great number of cases classified as ''unknown'' in the extended Wigglesworth and the modified Aberdeen were allocated a placental cause of death in the Tulip classification (Table 9).

Table 7
Classification by Morrison et al.: causes

Code	Classification	%	Subclassification	*n*
1.1	Hypoxia	55.6	Intra-uterine growth retardation	121
1.2			Cord accidents/compression	25
1.3			Maternal hypertension	11
1.4			Placental insufficiency	103
1.5			Postmaturity	–
1.6			Other	10
2.1	Antepartum haemorrhage	9.1	Major abruptio placentae	41
2.2			Placenta praevia	–
2.3			Significant unexplained antepartum haemorrhage	3
3.0	Congenital anomalies	6.0		29
4.1	Diabetes	2.9	Insulin dependent	7
4.2			Gestational	7
5.0	Miscellaneous	6.0		29
6.0	Trauma	–		–
7.0	Unclassified	19.2		93
8.0	Problematic classification	1.2		6
Total		100		485

Minimal subclassification of placental causes results in loss of specific information, non-specific counselling of parents on recurrence risks and hampers targeting adequate preventive strategies. In this respect the classifications by Hovatta et al., de Galan-Roosen et al. and Morrison and Olsen [23–25] seem unsatisfactory (Table 10). Use of placental subgroups triggers the discussion on definitions of these groups. Largest placental subgroup for the Tulip classification was ''placental bed pathology'' ($n = 166$, 34.2%), in 42 cases this cause of death was allocated due to an abruptio placentae, in 122 cases due to placental infarctions and in two cases both were present. Others also worked with the same cut-off point for infarctions [24,36]. Morrison and Olsen have a higher (25%) cut-off point [25]. Second largest placenta subgroup was ''placental pathology; development'' in 76 cases (15.7%). In 50 cases this cause of death manifested as placental hypoplasia. We assume that part of this group comprehends cases with ''placental bed pathology'' as cause due to sampling error [37]. Moreover, dependent on the references used for placental weight and placenta/birth weight ratios, allocation of placental hypoplasia can vary [18,38]. To improve validity of statistics, uniformity of definitions of these large placental subgroups are needed.

The classification by de Galan-Roosen et al. has been validated with a low percentage (7%) of unclassifiable cases [2]. However, several placental pathological entities are crudely divided into two groups only. Ninety-eight cases (20.2%) were allocated to ''placenta/cord pathology; acute/subacute'' and 118 (24.3%) cases to ''placenta/cord pathology; chronic/progressive''. The second problem we faced was the large group

Table 8
ReCoDe: relevant conditions

Code	Classification	%	Subclassification	*n*
A1	Fetus	53.0	Lethal congenital anomaly	28
A2			Infection	19
A3			Non-immune hydrops	19
A4			Isoimmunisation	–
A5			Fetomaternal haemorrhage	44
A6			Twin-twin transfusion	–
A7			Fetal growth restriction	147
B1	Umbilical cord	5.6	Prolapse	–
B2			Constricting loop or knot	6
B3			Velamentous insertion	6
B4			Other	15
C1	Placenta	26.4	Abruptio	30
C2			Praevia	–
C3			Vasa praevia	–
C4			Other ''placental insufficiency''	98
C5			Other	–
D1	Amniotic fluid	–	Chorioamnionitis	–
D2			Oligohydramnios	–
D3			Polyhydramnios	–
D4			Other	–
E1	Uterus	–	Rupture	–
E2			Uterine anomalies	–
E3			Other	–
F1	Mother	0.8	Diabetes	2
F2			Thyroid diseases	–
F3			Essential hypertension	–
F4			Hypertensive disease in pregnancy	–
F5			Lupus or antiphospholipid syndrome	2
F6			Cholestasis	–
F7			Drug misuse	–
F8			Other	–
G1	Intrapartum	–	Asphyxia	–
G2			Birth trauma	–
H1	Trauma	–	External	–
H2			Iatrogenic	–
I1	Unclassified	14.2	No relevant condition identified	50
I2			No information available	19
Total		100		485

allocated to ''problematic classification'' (108 cases). This was mainly due to the cases with >10% placental infarctions (death group: ''placenta/cord pathology; acute/subacute'') together with a small for gestational age fetus (''placenta/cord pathology; chronic/progressive''). Although cause and mode of death are relevant aspects of the pathophysiology of IUFD, these items are two separate entities which should not be merged into one.

Any classification system that results in a low proportion of cases with a known cause of death does not seem to be fulfilling its purpose. Due to differences in definition, it is difficult to compare the percentages of unexplained cases in the different systems. For the total percentage of unknown cause of death groups we studied the groups ''unknown'', ''unexplained'', ''unclassifiable'' and ''problematic classification'' together. The cause of death group ''unknown'' varied from 0% in the classification by Hey et al. to 88.7% in the extended Wigglesworth. A short classification system such as the extended

Table 9
Modified Aberdeen unexplained ($n = 293$) and problematic ($n = 4$) and extended Wigglesworth unexplained ($n = 429$) and problematic ($n = 1$) versus the Tulip classification

Tulip cause of death	Placental bed pathology	Placental pathology; development	Placental pathology; parenchyma	Umbilical cord complication	Placenta: not otherwise specified	Other: fetal hydrops of unknown origin	Other: maternal disease; diabetes mellitus	Other: maternal disease; other	Unknown: despite thorough investigation	Unknown: important information missing	Total
Modified Aberdeen											
Unexplained ≥2.5 kg	12	35	5		13				15	10	90
%	14	40	6		15				15	10	100
Unexplained <2.5 kg	75	26	7	5	12				60	18	203
%	37	13	3	2	6				30	9	100
Problematic classification	1		2							1	4
%	25		50							25	100
Extended Wigglesworth											
Unexplained antepartum fetal death	166	75	13	25	29	2	2	5	82	30	429
%	39	17	3	6	7	0.5	0.5	1	19	7	100
Unclassifiable			1								1
%			100								100

Table 10
De Galan-Roosen, Hovatta and Morrison and Olsen classifications versus the Tulip classification: placental causes ($n = 312$)

	Tulip placental cause, $n = 312$					
	Placental bed pathology	Placental pathology; development	Placental pathology; parenchyma	Umbilical cord complication	Placenta: not otherwise specified	Total
De Galan-Roosen et al.						
Placenta/cord pathology: acute/subacute	66	2	3	25	1	97
Placenta/cord pathology: chronic/progressive	14	74	10		18	116
Problematic classification	86		3		10	99
Hovatta et al.						
Abruption of the placenta	38					38
Large placental infarction	102				1	103
Cord complication				25		25
Other placental feature; severe pre-eclampsia	4	1				5
Other placental feature; other causes	15	74	11		25	125
Fetal bleeding; fetomaternal transfusion			5			5
Fetal bleeding; other bleeding		1				1
Unexplained	6					6
Problematic classification	1				3	4
Morrison et al.						
Hypoxia; intra-uterine growth retardation	79	20	3		7	109
Hypoxia; cord accidents/ compression				25		25
Hypoxia; maternal hypertension	9	1				10
Hypoxia; placental insufficiency	33	43	7		17	100
Hypoxia; other	1	2	4		1	8
Antepartum haemorrhage; major abruptio placentae	41					41
Antepartum haemorrhage; significant unexplained APH	1	1				2
Diabetes; insulin dependent		2			1	3
Diabetes; gestational		5			1	6
Miscellaneous			2			2
Problematic classification	2	2			2	6

Wigglesworth may seem preferable but remains too general. This system only has cause of death groups for malformed stillbirths, stillbirths with clear microbiological evidence of infection or with hydrops fetalis. All other stillbirths are classified in the group ''unexplained antepartum fetal death''. Nevertheless, as is shown in Table 9 cause of death is evident for a large group of these stillbirths. For the classification by Hey et al. no deaths were classified as ''unclassifiable'' or ''unknown'', however, 88.4% of cases were allocated to the group ''asphyxia antepartum''. In our opinion asphyxia is not a cause of death but a clinical condition which is the result of an underlying cause of death and can be defined in many cases [4]. Similarly in the system of Hovatta et al. 8.3% of cases were classified as ''asphyxia for unexplained reasons''. In fact these cases should be added to the cause of death group ''unknown'' and, therefore, their percentage of ''unknown'' increases from 21.6% to 29.9%. This also accounts for the group ''hypoxia; intra-uterine growth retardation'' in the system by Morrison et al. (24.9%). As is shown in Table 10 most of the ''asphyxia and hypoxia related'' causes have placental pathology as underlying cause of death. A large group of unexplained IUFD's is often due to design of the system itself and lack of amendment of the system to present insight into pathophysiology of IUFD. In 23.3% of cases the cause remained ''unknown'' for the Tulip classification (Table 1). In about two thirds of deaths the cause remained ''unknown'' because important information was missing. This suggests that many of these deaths may be under investigation rather than truly unexplained. Although some systems aim to classify underlying cause of death, mechanism of death and risk factors are

often mixed [39]. Cause of death groups should consist of pathophysiological entities. Many systems consist of cause of death groups that encompass clinical conditions such as pre-eclampsia [21], antepartum haemorrhage [25], breech presentation [21] and intraventricular haemorrhage [22]. Similarly intra-uterine growth restriction is a clinical condition of several causes of death, see Table 10.

Recently Gardosi et al. [3] published their ReCoDe classification that seeks to establish relevant conditions at death considering mother, fetus and placenta. Their system has evoked a new discussion on classification as they do not classify cause of death. The system is easy to use, as panel sessions are not needed, with retainment of important information. However, guidelines for the ReCoDe classification are less clear and this resulted in confusion of allocation of relevant conditions. Hierarchy underestimates the importance of some of the items in the lower part of the system. Results of our cohort presented in Table 8 are comparable to the stillbirth cohort presented by Gardosi et al. Largest relevant condition for our group was fetal growth restriction (30.3%) compared to 43.0% [3]. In our IUFD cohort 14.2% of cases were unclassified versus 15.2% [3]. We agree with Gardosi et al. that these relevant conditions give insight into the death. However, if classification of the underlying cause of death is added more insight is warranted. For the Tulip classification 27.6% of cases in the placental group were small for gestational age at birth versus 8.7% in the other cause of death groups illustrating diversity in cause of death for these small fetuses. Recording of growth restriction as a contributing factor is nevertheless important for management and counselling of future pregnancies.

In conclusion, comparison of seven classification systems for cause of death and one system for relevant conditions applicable for the IUFD group illustrated different problems during use. Largest cause of death group for IUFD was placental pathology, and largest contributing factor was growth restriction. This illustrates the vital role of the placenta in determining optimal fetal development. Internationally used systems without placental cause of death groups or minimal subdivision of this group are in our opinion not useful in modern perinatal audit. Systems with a low proportion of known causes of death or cause or death groups consisting of clinical manifestations of pathophysiological entities are not useful either as this results in loss of information. Of the systems we compared the Tulip classification met the requirements for a useful classification best. This classification is currently in use in the Netherlands for national audit studies [40]. International use of the same classification system for cause of death will facilitate comparison of statistics. Future classification efforts and research should be aimed at further definition of the placental cause of death groups, investigation into the differences in clinical manifestations of placental causes of death and the prevention of these deaths.

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